

## Lumbar to Sacral Nerve Rerouting to Restore Voiding in Spina Bifida

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## Disclosures

- No relevant financial disclosures

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## Myelomeningocele

- The neurologic lesion produced by this condition can be variable, depending on what neural elements, if any, have everted with the meningocele sac. *The bony vertebral level often provides little or no clue to the exact neurologic level or lesion produced.*
- The neurologic lesion produced by this condition influences lower urinary tract function in a variety of ways and cannot be predicted just by looking at the spinal abnormality or the neurologic function of the lower extremities.

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## Phenotypes

- synergic (26%)
- dyssynergic with and without poor detrusor compliance (37%)
- complete denervation (36%)

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## Specific Concerns

- 1) Safety
  - Obstruction
  - Pressure
  - Emptying
- 2) Social function
  - Continence



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## Phenotypes

- Categorization of lower urinary tract function in this way has been extremely useful because it reveals:
  - which children are at risk for urinary tract changes
  - who should be treated prophylactically
  - who need close surveillance
  - who can be monitored at greater intervals

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## Spina Bifida – State of the Art

- Low Pressure Storage
- Continence
- Function



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## Neuromodulation



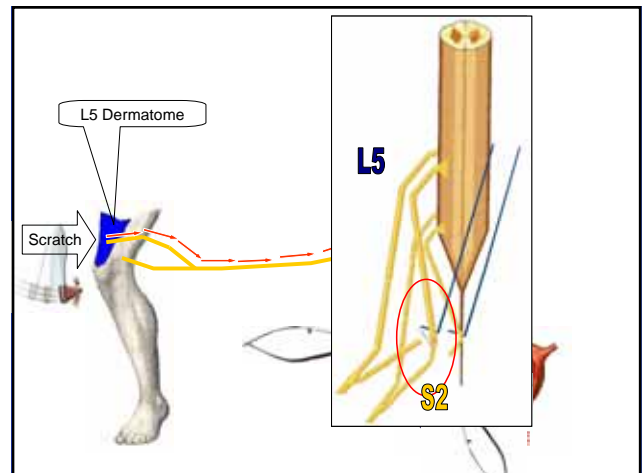
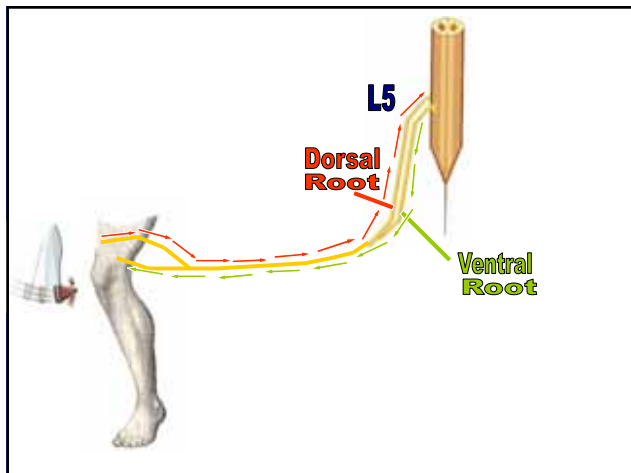
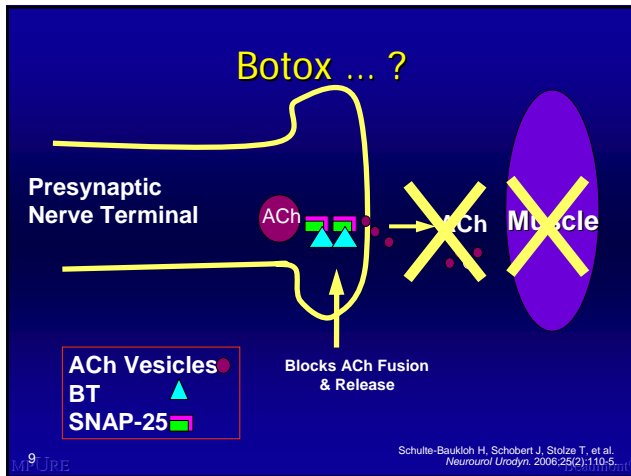
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## Xiao Animal Studies

### ■ Bench to Bedside

- Rat Studies – Late 1980s
  - L4 to L6 Anastomosis
  - Bladder contraction with electrical stimulation
  - Neural Tracing (HRP)
    - Somatic motor axons regenerated successfully into the pelvic nerve
    - Bladder was reinnervated by the L4 motor neurons
  - New concept: the impulse delivered by the efferent neurons of a somatic reflex arc can be transferred to initiate responses of an autonomic effector

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## Xiao Animal Studies

### ■ Bench to Bedside

- Higher animal experiments:
  - Continued experiments focused on the underlying mechanism of the somatic-autonomic reflex pathway for micturition
  - Pharmacological studies:
    - New nerve pathway mediated by cholinergic transmission
      - Nicotinic and Muscarinic Receptors
    - Because the same neurotransmitter is released, somatic reflex activity can be transferred to the bladder smooth muscle and cause a detrusor contraction
    - Can induce reflex in intact animal and after acute spinal cord injury

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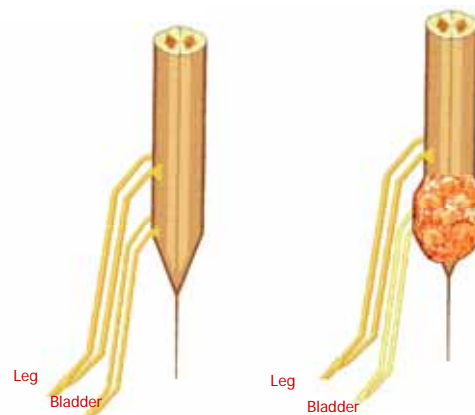
## Xiao Human Studies – Spinal Cord Injury

- Spinal Cord Injury – J Urology 2003
  - 15 Males – Hyperreflexic Bladder and DESD
  - 67% success
  - Synergistic Voiding

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### Expanding the Xiao Concept to



## Xiao Human Studies – Spina Bifida

- Spina Bifida – J Urology 2005
  - 20 Children – 14 Areflexic, 6 Hyperreflexic NGB
  - 85% success
- Update – European Urology 2006
  - 92 Spinal Cord Injury, 88% success
  - 110 Spina Bifida, 87% success

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## The Beaumont Experience



## Beaumont Experience

- Patient selection
- Pre-operative evaluation
- Surgical approach
- Post-operative care
- Post-operative follow-up
- Potential complications
- Definition of success

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## Beaumont Experience

- Patient selection
  - Age 6 or greater
  - Neurogenic bladder on CIC
  - Intact lumbar nerve roots based on EMG testing
  - Upper extremity motor function

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## Study Design

- Lower Extremity
  - Neurological Exam
  - EMG / Nerve Conduction Studies
- Bladder
  - Questionnaires
  - CMG / Pressure-Flow
  - Cystoscopy / RBUS / Labs
  - Reflex Arc Stimulation
- Bowel
  - Questionnaires

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## Beaumont Experience

Pre-operative evaluation

- MRI
- Neurological Exam
- EMG / Nerve Conduction Studies
- Cystoscopy
- Urodynamics
- BUN/Creat



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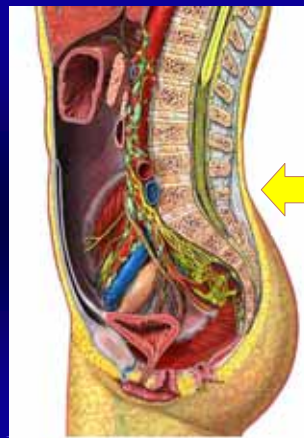
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## Difficult Surgical Approach



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### Spinal Cord Injury

Below spinal cord at level of cauda equina

Laminectomy performed to access the dura

Dura opened allowing access to the cauda equina nerve roots

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## Spina Bifida



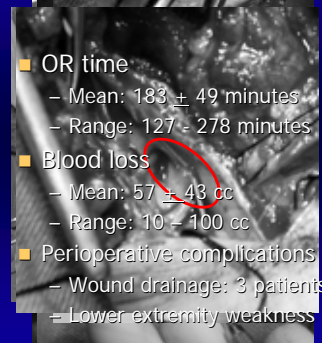
Much more challenging

Often tethered cord

Approach is different

## Beaumont Experience: Operation

- 9 spina bifida patients treated
- Prone position
- Limited laminectomy
- Open dura
- Expose cauda equina
- Donor and recipient root identification
- End-to-end sutured anastomosis
- OR time
  - Mean:  $183 \pm 49$  minutes
  - Range: 127 - 278 minutes
- Blood loss
  - Mean:  $57 \pm 43$  cc
  - Range: 10 - 100 cc
- Perioperative complications
  - Wound drainage: 3 patients
  - Lower extremity weakness



## Beaumont Experience

### Post-operative care

- Perioperative antibiotics (Amp / Gent)
- Bedrest x 48 hours
- Monitor for dural leak
- Neurovascular checks
- Advance diet as tolerated
- Home on oral pain medication, stool softener and oral antibiotics

## Beaumont Experience

### Post-operative follow-up

- Neurological Examination
  - 1 month, 1 year
- Urodynamic Testing / Dermatome Stimulation
  - 3, 6, 9, 12, 18, 24, 36 Months
- Ultrasound
- Laboratory Monitoring

## Patient Characteristics

### ■ 9 Patients

- 3 males
- 6 females

### ■ Spina Bifida

### ■ Age

- Median: 8 years
- Range: 6 to 37 years

### ■ Ambulatory Status

- AFOs: 5 patients
- Forearm crutches: 2 patients
- No assistance: 4 patients

### ■ No prior major bladder surgery



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## Baseline Characteristics

Pt	Age yrs	Ht. in	Wt lbs	Level	Closed	VP	T Cord	Anti mus	stress	urge
1	6	45	39	S3	N/A	N	N	N	Y	N
2	7	51	62	L5/S1	In-utero	Y	Y	Y	N	Y
3	13	53	136	L3/L4	Birth	Y	Y	Y	N	Y
4	7	51	87	L3	In-utero	N	N	N	Y	Y
5	6	45	58	S3	Birth	N	N	Y	Y	N
6	17	63	110	L4	Birth	Y	Y	N	N	Y
7	8	49	63	L5	In-utero	Y	N	Y	Y	Y
8	7	45	51	L3/L4	Birth	Y	N	Y	Y	Y
9	37	72	155	L4	Birth	N	Y	N	N	Y

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## Outcomes

### ■ Hospitalization

- Mean Length of Stay: 3.4 (2-7) days
- Perioperative Complications (30 days):
  - Foot Drop – 1 Patient
  - Wound Drainage – 3 Patients
  - Prolonged Inability to Bear Weight – 1 Patient

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## Perioperative Data

Pt	Donor Side	Donor Level	Recep. Side	Recep. Level	OR Time (min)	LOS (days)
1	Left	L5	Left	S2/S3	197	3
2	Left	L5	Left	S1/S2/S3	150	4
3	Left	L3	Left	S3	278	7
4	Right	L3	Left	S2	244	2
5	Left	S1	Bilateral	S3	150	2
6	Left	L5	Left	S2	157	3
7	Right	L2	Left	S2/S3	181	3
8	Left	L3	Left	S2/S3/S4	127	4
9	Left	S1	Left	S2/S3	156	3

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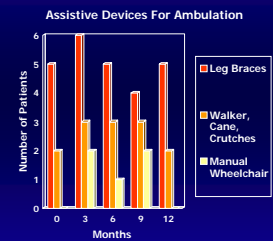
## Early Outcomes

### ■ Interesting Stories...

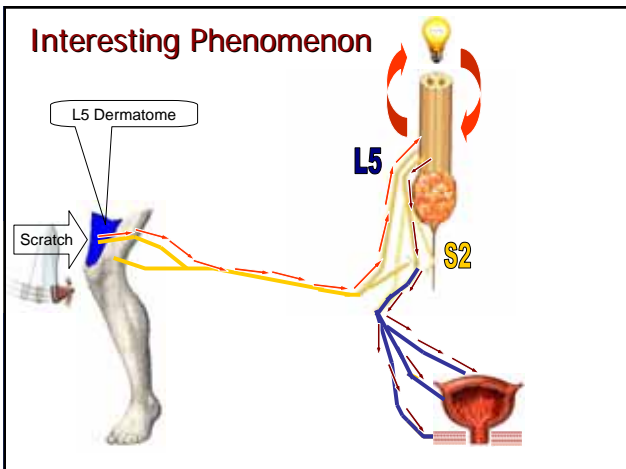
- Bowel/Bladder Neurological Changes
  - Sudden Worsening of Urinary and/or Fecal Incontinence
  - Improved Continence
  - Ability to Initiate Voiding

## Outcomes: Lower Extremity

- Early
  - 8/9 weak
- 1 Year
  - 8/9 at or near baseline
  - 1/9 with foot-drop



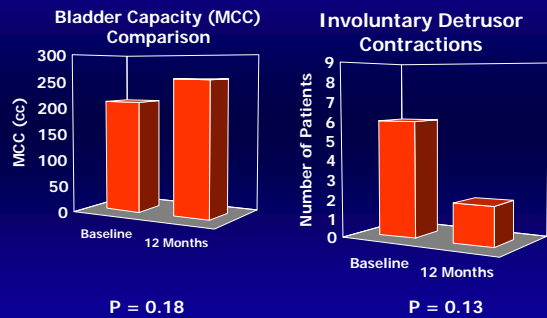
## Interesting Phenomenon



## Voiding and Urodynamic Data

	MCC		IDC		Sensation of Filling?		Antimuscarinic		Reflex?	Voiding?
Pt.	BL	12m	BL	12m	BL	12m	BL	12m	Y/N	Y/N
1	252	180	No	No	No	Yes	No	No	No	Yes
2	200	402	Yes	No	Yes	Yes	Yes	No	Yes	Yes
3	165	210	Yes	No	Yes	Yes	No	No	Yes	No
4	200	269	Yes	No	Yes	Yes	No	No	Yes	Yes
5	48	192	No	No	No	No	Yes	No	No	Yes
6	350	393	No	No	Yes	Yes	No	No	Yes	Yes
7	226	214	Yes	Yes	Yes	Yes	Yes	No	Yes	No
8	189	155	Yes	No	Yes	Yes	Yes	No	Yes	Yes
9	269	268	Yes	Yes	Yes	Yes	No	No	Yes	Yes

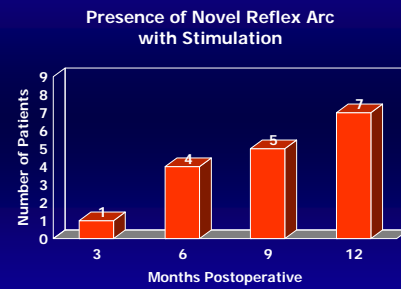
## Outcomes: Bladder



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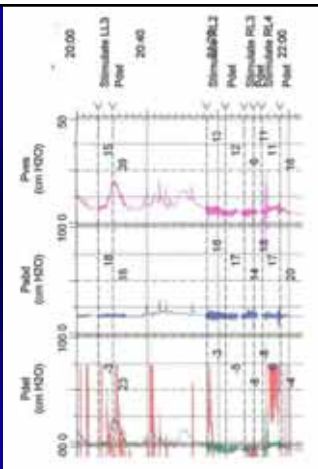
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## Outcomes: Bladder



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## Outcomes: Bladder

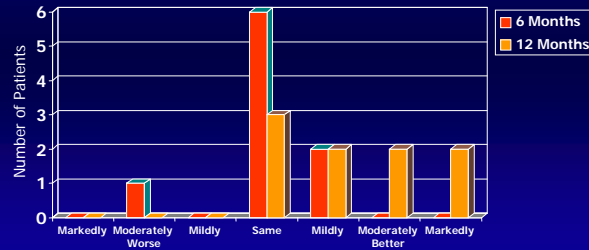
- Number Voiding
  - Preoperatively: n=2
  - 12 Month Urodynamic Testing
    - Voided: n=7
    - Mean Voided Volume =  $133 \pm 75$  cc (50-250)
    - Mean PVR =  $119 \pm 125$  cc (10-380)
    - Mean Qmax =  $10 \pm 8$  cc/sec (4-25)
- Number Catheterizing
  - 12 Month Questionnaire:
    - 7/9 still using catheter

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## Outcomes: Bowel

Change In Ability to Move Bowel



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## Global Response

Patient:	1	2	3	4	5	6	7	8	9
Since having surgery how has the ability to move your bowels changed?	Markedly Better	Markedly Better	Moderately Better	Same	Slightly Better	Same	Same	Slightly Better	Moderately Better
Since having surgery how has the ability to void changed?	Markedly Better	Same	Same	Slightly Better	Slightly Better	Same	Same	Moderately Better	Same
Since having surgery how has your quality of life changed?	Markedly Better	Same	Slightly Better	Same	Same	Same	Same	Moderately Better	Slightly Worse
Knowing what you know now, would you undergo the surgery again?	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes

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## UPDATE

- Recently finished 2 year follow-up
- Currently 4 of 9 off catheterization
- Bowels improved in most
- Incontinence still problem in some
- Recently performed the rerouting procedure on 4 more children
- Dr. Gilmer joined our research team and was integral in performing the procedure in May 2009

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## Lessons Learned

- Patient Selection:
  - Intrauterine closure of myelomeningocele associated with:
    - Longer operative times
    - Worse intraoperative scar tissue
    - Greater lower extremity weakness postoperatively
- Pre-operative neurological testing
  - Requires intact lumbar donor nerve
    - Patients using crutches may be at increased risk of conversion to chair
    - Higher lesions may require nerve graft

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## Conclusions

- First North American trial in spina bifida demonstrating return of bladder and bowel function with nerve rerouting
- Early results show improvement in bladder and bowel function that may have a major impact on quality of life in patients with spina bifida
  - No patient on anticholinergic
  - 2/9 off catheterization at 1-year, 4 of 9 off cath at 2 years
  - 7/9 with novel reflex present
  - 9/9 voiding and/or have a novel reflex
- Foot drop present in 1 patient
- Follow-up ongoing for 3 years
- Crucial to do this under rigorous research protocol given the potential risks. Should not be offered as standard of care until more data is available!

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## Future Directions

- Novel Micturition Centers
  - Functional MRI
- Preventing Lower Extremity Complications
  - Donor rootlet separation and identification
  - End-to-side anastomosis
- Nerve Growth Factor
  - ? Can be administered by injection stem cells at the time of the anastomosis



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## Special Thanks to: Beaumont

William Beaumont Hospital

- CG Xiao, MD - Nerve Rerouting Pioneer
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- Holly Gimer, MD
- William Nantau, Brian Bush- Clinical Neurophysiology
- Gary Trock MD-Neurology
- Cindy Turzewski – Study Coordinator
- Our Patients



## Questions?



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